REMARKS

1. Status of the Claims

1.1. The examiner questions the status of claims 103-119. Claims 103-105 were not part of the application as entered into the US national phase, but were first presented in the September 10, 2008 amendment, and later cancelled. Claims 106-119 were not presented in the US national phase prior to the present office action.

The PCT application as filed had 119 claims. In the course of international preliminary examination, the first written opinion replaced the original claims set with a 112 claim set, as is proper under PCT practice. When we filed our request for US national stage entry, we specifically enclosed a "courtesy copy of the February 22, 2005 response to first written opinion with annexes with claims 1-102 to be substituted for original claims 1-119 for examination in this case." This is a routine request under US national stage practice and means that **US examination commenced with the 102 claim IPE claims set.** The preliminary amendment dated January 27, 2006 was directed to that 102 claims set. It did not even refer to claims 103-105, let alone cancel them as asserted by the examiner.

New claims 103-105 were presented by the September 10, 2008 amendment but subsequently cancelled. No claim number higher than 105 has previously been presented to the PTO for examination in this case. (The instant amendment presents the claims numbered 106-111 for the first time in this national phase prosecution.)

1.2. In response to OA s10, we have converted claims 21-23, 27, and 29 and 28 into method-of-use claims dependent on method claim 43, and claims 27-31 into method-of-use claims dependent directly or indirectly on method claim 43. Since method claim 43 is withdrawn, we have marked the amended claims as withdrawn, too.

1.3. In response to the objections stated in OA ss14-17, claims 19, 20, 25 and 32 have been amended.

A) claim 32 to cite "different, spatially encoded beads" instead of "different, spatially encoded, beads".

B) claim 19 and 20 to use proper Markush language as suggested by the Examiner.

C) claim 25 by adding a comma between "polyacrylates" and "polyacrylamides".

1.4. We have noted that withdrawn method claims 49 and 53 referred to the "library" of claim 32, rather than the "composition" of claim 32; this has now been corrected.

2. Right of Priority (OA s7)

2.1. We do not understand the logic of the examiner's position that this application, which as admitted in OA s5 is the national stage of PCT/DK03/00635 and thus has the same specification, original claims, and drawings as that application, is not entitled to the benefit of the filing date (September 26, 2003) of the PCT application. This application, while accorded a US serial number and a nominal US filing date corresponding to the date that requirements for US national stage entry were completed, is not a separate application from the PCT application but rather merely the national phase of that application.

Under 35 USC 363, "an international application designating the United States shall have the effect, from its international filing date ..., of a national application for patent regularly filed in the Patent and Trademark Office except as otherwise provided in section 102(e) of this title." The 102(e) exception relates to the prior art effect of this

application against later applications by others and has no bearing as to the effective date of this application for assessing the patentability of its own claims.

We therefore respectfully submit that all claims are at least entitled to the international filing date of September 26, 2003.

2.2. With regard to entitlement to the dates of the provisional applications, we respectfully submit that at least claims 19 and 20 are entitled to the benefit of DK PA200201444 and US 60/413,771 and thus to a date of September 27, 2002.

Claim 19 is based on original claim 75 in PA200201444/US 60,413,771 cited herein below:

> "A beaded or granulated polymer according to any of claims 18 and 19 where the fluorescently detectable marker is selected from the group consisting of dyes based on the structure of fluorescein, oregon green, rhodamine, aminobenzoic acid, AlexaTM probes, BODIPY-dyes, cascade blue dye, coumarine, naphthalenes, dansyl, indoles, pyrenes pyridyloxazole, cascade yellow dye, Dapoxyl Dye,Fluorescamine, aromatic ortho dialdehydes, OPA and NDA, ATTO-Tag's, 7-Nitrobenz-2-Oxa-1,3-Diazole or derivatives thereof"

Claim 20 is based on page 14 lines 12 to 15 cited herein below:

> "Fluorescently detectable markers are preferably selected from the fluorescent group of compounds and materials consisting of fluorencent organic polycyclic compounds, conjugated vinylic compounds, heterocyclic transition metal complexes, rare earth metal compounds, inorganic oxides and glasses".

3. Election/Restriction (OA s3)

3.1. We have previously elected, with traverse, Group II

(claims 32-42). Group I (claims 2-31) is rejoined due to the claim amendments filed on September 10, 2008 and the petition decision of May 15, 2009.

In the petition decision QAS Julie Burke state that "species of particle number, marker, detection, and polymer are all obvious variants of each other". We are requested to state if we disagree with this assumption.

Applicants do not agree that "species of particle number... are all obvious variants of each other."
In the case of species of particle number, applicants are arguing that in fact the number of particles per bead is an important limitation in distinguishing the art presently relied on.

At the present time, applicants are not arguing that the choice of polymer, marker, or type of detection is relevant to avoiding obviousness.

3.2. The Examiner states that withdrawn process claims that depend from or otherwise include all the limitations of an allowable product claim will be rejoined in accordance with the provisions of MPEP§ 821.04.

We note that method claims 43, 49 and 53 are all directly dependent on composition claim 32, and the remaining method claims are thus indirectly dependent on composition claim 32. Claim 79, which is dependent on 53, additionally explicitly recites the compositional limitations of composition claim 32. In view of the dependency, we think the explicit duplication of these limitations in the preamble of claim 79 is superfluous but await the examiner's guidance as to whether to leave them in or delete them.

4. Definiteness Issues

4.1. The Examiner questions **(OA s26)** use of the term "essentially" in the following claims:
- claim 32 citing "essentially each bead is individually

identifiable"
- claim 10 citing "essentially spherical"
- claim 11 citing "essentially the same diameter"
- claim 12 citing "essentially monodisperse".

The specification cites the following relevant definitions (page 15 line 30 to page 16 line 12):

Essentially: This term signifies that a physical process often yields a result that deviates from the theoretical result expected due to inheterogeniety and incomplete control of the process.

Essentially monodisperse: This indicate that a slight tendency towards inhomogenous location of particles can be expected due to differences in density and aggregation phenomena.

Essentially spherical: Any spherical object for which the distance from the gravitational centre to any point on the surface of the object is in the range of from a quarter of the average distance from the gravitational centre to the surface to preferably less than four times the average distance from the gravitational centre to the surface.

Essentially the same diameter: The diameters are never identical since a gaussian distribution of bead sizes is obtained during polymerization.

In *In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983), a product-by-process claim recited "adding a metal oxide, metal hydroxide, metal sulfate, metal nitrate or hydrated metal oxide and a silicon dioxide source that is essentially free of alkali metal to a 5 to 90% strength aqueous solution of hexamethylenediamine to form a mixture

that is essentially free of alkali metal..." and subsequently forming a crystalline metal silicate that was "essentially free of alkali metal".

The cited prior art taught a process in which the mole ratio of alkali metal to silica in the reaction mixture was 0.01:1-3.0:1. (The molar ratio of 0.01 corresponded to 3819 ppm sodium.) Marosi relied solely on the virtual absence of sodium in their starting materials (in one example the level was 4 ppm) to distinguish the reference.

The Board affirmed the rejection of "essentially free" as indefinite. In its brief to the Court, the PTO said, "[W]e challenge appellants to show on this record where one skilled in the art would draw the 'essentially free of alkali metal' line between 4 ppm and 3,819 ppm."

The Federal Circuit reversed. "Insofar as it requires appellants to specify a particular number as the cutoff between their invention and the prior art, the PTO's position is impractical.... " It cited with approval the CCPA decision of *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975), holding that "substantially increase" was definite, and applied the same standard as did the Mattison court:

> As in appellants have provided a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine whether a process uses a silicon dioxide source "essentially free of alkali metal" to make a reaction mixture "essentially free of alkali metal" to produce a

zeolitic compound "essentially free of alkali metal." We are persuaded that such a person would draw the line between unavoidable impurities in starting materials and essential ingredients.

Marosi is cited with approval in MPEP 2173.05(b)(B), and *Mattison* in 2173.05(b)(D).

4.2. The examiner also questions (OA s27) the use of trademarks in claim 19. The examiner cites *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982), as establishing that a trademark cannot be used in a claim as a limitation to identify or describe a particular material or product. However, such was not the holding of the Board. Simpson had asserted that the claim limitation "Hypalon membrane" encompassed "every synthetic resin". The Board was of the opinion that this created uncertainty as to the meaning of Hypalon, as it otherwise could be construed "very narrowly" as drawn to "a particular chlorosulphonated ethylene having a specific group of additives employed by the owner of the 'Hypalon' trademark to produce the desired properties".

The present applicants have not urged that the trademarked products recited in claim 19 be interpreted as referring to anything other than the products to which those trademarks were applied as of the filing date of this application. Hence, *Simpson* does not justify rejection of claim 19.

5. Written Description (OA s24)

Claims 2, 3, 7-12, 17-40 and 42 are rejected as failing to comply with the written description requirement. The Examiner specifically requests indication of basis for "wherein the diameter of the particles is less than 30 micrometer". This term appears in claim 32, and it is believed that the other claims are rejected for lack of written description solely because they are dependent, directly or indirectly, on claim 32. We traverse.

Claim 32 is based on the following:

- original claim 44 citing:
"A composition comprising a plurality of different, spatially encoded, beads according to any of claims 1 to 43, wherein

essentially each bead is individually identifiable".

- original claim 91 citing:
"the size distribution of the beads is in the range of from 0.1 millimeter to preferably less than 2 millimeter, such as about 0.5 millimeter" and "the diameter of the particles is preferably **less than 30 micrometer**"

- page 33 lines 13 to 15 citing:
"Each beaded or granulated polymer matrix preferably comprises at least 2 particles, such as at least
3 particles, for example at least 4 particles, and preferably 10 or less particles".

- page 1 lines 12 to 13 citing:
"The present invention relates to a spatially encoded polymer matrix in the form of a bead"

There is thus clear basis for the questioned limitation of claim 32.

6. Double Patenting Provisional Rejection (OA s33-37)

Claims 2, 3, 7-12, 17-40 and 42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3-10 and 59 of the co-pending Application No. 11/631,181 (Spherical radiofrequency-encoded beads; Søren Christensen) and claims 94 and 96 of co-pending Application No. 10/566,757 (Triangulenium fluorescent dyes and polymers comprising such dyes; Bo Wegge Laursen).

We repeat our request that the "provisional rejection" be held in abeyance until either 1) all other issues in this case are resolved, or 2) one of the reference applications is issued, i.e., there is cause to convert the provisional rejection into a real rejection. To "hold in abeyance" is not

to withdraw the provisional rejection, it is merely that applicant need not make a substantive response, i.e., file a terminal disclaimer or explain why the rejected claims (with or without amendment) are not obvious over the reference claims.

The examiner states that a rejection cannot be held in abeyance. That's true, but there's no rejection here. Rather, there is merely a "provisional rejection". A provisional rejection is merely notice by the USPTO of its intent to make a rejection if one of the reference applications becomes a patent. See MPEP 804(I)(B). MPEP says that "the merits of such provisional rejection **can** be addressed by both the applicant and the examiner without waiting for the first patent to issue." In law, "can" is not mandatory.

The provisional rejection is withdrawn if the reference application is abandoned, or the claims of either application changes so as to avoid the conflict. Pursuant to 804(I)(B)(1), if the "provisional" rejection is the only issue remaining in the earlier filed application, the provisional rejection must be withdrawn.

The instant application is 10/529,397 whereas the reference applications are 11/631,181 (OA s34) and 10/566,757 (OA s36). Plainly, the instant application is the earlier-filed application. Hence, if we are able to overcome the other rejections in this case - as we believe we have - the provisional rejection should be withdrawn in accordance with MPEP 804(I)(B)(1).

7. Novelty Issues (OA s29)

Claims 2, 3, 7-12, 17-32, 38-40 and 42 stand rejected as allegedly anticipated by Trau et al. WO 99/24458. We traverse.

We assume that the examiner considers the "polymeric carrier" and the "reporter beads" (microparticles) disclosed in WO 99/24458 to be, respectively, the "bead" and the "detectable particles" cited in claim 32. In addition, we

believe that in Trau the number of markers is identical to the number of reporter beads.

The number of particles

The beads in the composition of claim 32 each provide from 3 to not more than 10 spatially immobilized, individually detectable particles.

WO 99/24458 does not disclose that the polymeric carrier provides from 3 to not more than 10 markers.

In Trau Figure 6, the polymeric carriers (beads) are represented as large open circles of diameters on the order of 100 microns, and the attached reporter beads (particles) are represented as small shaded circles, with a small "R" (red) or "G" (green) superimposed to indicate the fluorescence of the fluorophores associated with the reporter beads. All of the represented polymeric carriers have at least 20 attached reporter beads.

Figure 7 is similar, but there is a third type of reporter bead, marked "YR" (yellow red"). The number of reporter beads (particles) per polymeric carrier (bead) is if anything greater than in Figure 6.

Figure 8 is like Fig. 7, but the third type of reporter read is this time "B" (blue).

The Trau specification comments:

> FIG. 6 is a schematic diagram of red-tagged and green-tagged carriers, combined to form Population 3 in Procedure D in Example 3 hereinafter. For clarity, the reporters drawn here are much larger than the 1 pm reporters used in the Example;
>
> FIG. 7 is a schematic diagram of Population 4 in Procedure E in Example 3. For clarity, the reporters drawn here are much larger than the 1 pm reporters

used in the Example;

FIG. 8 is a schematic diagram of Population 5 in Procedure E in Example 3. For clarity, the reporters drawn here are much larger than the 1 um reporters used in the Example;

The carriers are further described in Example 1 as being 100-200 mesh [the US 100 mesh has an opening 0.149 mm, and 200 mesh of 0.074 mm, see http://www.azom.com/details.asp?ArticleID=1417], the reporters are further described in Example 2 as being fluorescent silica microspheres of one micron diameter, each tagged red or blue or green or yellow/red combination, and the tagged library is prepared in Example 3 by dividing the carriers into two portions and reacting each portion with one of the two fluorescent types of reporters. "FIG. 6 is a schematic of the red-tagged and green-tagged beads in Population 3."

In the Trau examples, 100 mg of carrier are reacted with 10 mg of fluorescent microspheres. If the densities are similar, then since the diameters are in the ratio of at least 74:1 (0.074 mm/1 micron), the volumes are as the cube of that ratio, hence since the total mass of carrier is 10 times the total mass of microspheres, the ratio of the number of microspheres to the number of carriers should be approximately $74^3/10$:1, or 40,522:1. Of course, that doesn't mean that all of the microspheres will become attached, but clearly we are far away from the 10 particles/bead maximum of claim 32.

The surface area of the carrier is $4*PI*R^2$ where R is the radius of the carrier; ignoring the curvature of this surface (since the microspheres are so much smaller than the carrier), the attached microspheres each take up $PI*r^2$ of this area, where r is the radius of the microsphere; the maximum packing density of circles on a plane surface is 0.9069, with the

circles arranged in a hexagonal lattice. This suggests that each carrier could carry as many as $0.9069 * 4 * 74^2 = 19,865$ microspheres.

Again, we don't assert that they in fact carry this many, but rather wish to show how unlikely it is that they are within the 3-10 range specified by claim 32.

Individually identifiable beads

The beads in the composition cited in claim 32 are - in contrast to the beads disclosed by Trau - "individually identifiable".

"Individually identifiable" is defined in the application as filed on page 18 lines 10 to 19 cited herein below:

> *"Uniquely identifiable: Used herein interchangeably with "individually identifiable", i.e. that a single bead can be identified on the basis of the spatial configuration of the particles immobilised in the bead. The encoded beads are "individually identifiable" within the limits of statistical probability of occurrence of identical beads and resolution of identification method. In one embodiment, with a practical resolution of 1:100 and only 4 encoding particles the probability of e. g. selecting two identical beads is 10^{-6} according to Monte-Carlo simulation. A total of ~10^{15} different beads may be encoded. More preferably, more than 95%, such as more than 97%, for example about or more than 98%, such as about or more than 99% of all beads will be "individually identifiable" under practical circumstances".*

The spatial immobilisation of the 3 to 10 particles in each bead is unique. Accordingly, the spatial positions of particles in each bead can be described by a set of

coordinates - i.e. a unique fingerprint which enables identification of unique beads in a population of beads.

WO 99/24458 asserts "each molecule in the library will have a unique signal associated therewith which signal is dependent on different combinations of markers to facilitate direct identification of each molecule" (page 8 lines 18 to 28). However, the standard of uniqueness does not measure up to that required by our definition of "individually identifiable".

Trau contemplates that in synthesizing the library, if the nascent molecule is reacted with a particular chemical group, the carrier will also be associated with a reporter bead that "has a marker associated therewith to identify the chemical group attached to the carrier." Thus, if the reactant is X, the red-tagged particles are attached, and if it's Y, the green-tagged particles are attached.

These libraries are characterized by the use of, first, a large number of different chemical groups, and second, the incorporation of the chemical groups at several different positions. A simple example would be a library of four members (XX, XY, YX, YY), in which each of two positions could have each of two chemical groups (X and Y).

By Trau's methodology, the molecule XY (or YX) may thus be distinguished from the molecules XX or YY by virtue of the relative strength of the red and green fluorescence of the bead.

Trau represents that these markers also "identify the position in sequence of the chemical group relative to other chemical groups in each molecule". However, Trau does not explain how the molecules XY and YX would be distinguished.

Trau exercises no control over where, on the surface of the carrier, the reporter bead attaches. Hence, the position of the reporter bead on the surface of the character does not encode the nature of the associated chemical group.

We may speculate as to how one might build upon Trau's

teachings in order to distinguish XY and YX. We do so with the caveat that such "building" goes beyond what is permissible in adjudicating anticipation, and it remains to be seen whether it even would have been obvious to a person of ordinary skill in the art.

How then does one distinguish XY and YX? One approach would be to use different markers for X and Y in each step, e.g. red and green for X and Y in step 1, vs. blue and yellow for X and Y in step 2. This appears to be what Trau contemplates by stating "each reporter bead has **a** marker associated therewith to identify the chemical group attached to the carrier **as well as** to identify the position in sequence of the chemical group relative to other chemical groups in each molecule...." A "combination of markers", e.g. red and blue, would then be indicative of a combination of groups in different positions.

It is quite evident that except in trivial situations, the number of unique molecules to be identified will exceed the number of unique markers available. Only four markers (red, green, blue and yellow) are explicitly disclosed by Trau. Even if this is deemed to satisfy the "individually identifiable" requirement as to claim 32 (albeit for just four beads), claim 33 requires that we be able to individually (i.e., uniquely) identify 100 different beads. There is no disclosure in Trau of 100 distinguishable markers.

Trau can identify a larger number of chemical groups if each is identified by a combination of markers. With the four markers red, green, blue and yellow, we have the four "solo" markers, 6 combinations of two colors, 4 combinations of three colors, and one four-color combination, and one absence of any color. That's a total of 16 possibilities, still well short of the 100 required by claim 33.

Moreover, if we wanted to identify four chemical groups at each of two positions, we can't simply use four markers at each synthetic step, since we then couldn't distinguish the

order of addition. Rather, we would have to divide the carriers into as many aliquots as there would be different molecules in the library, and react each aliquot with the appropriate combination of colors.

Alternatively - and we do not concede that this is taught or suggested by Trau - one could vary the proportions of the markers for X and Y in each step. Thus, in step 1, X could be all red and Y all green, whereas in step 2, X could be 75% red 25% green, and Y the reverse. If so, then the four dimers are encoded as follows:

XX=87.5% red 12.5% green
XY=62.5% red 37.5% green
YX=37.5% red 62.5% green
YY=12.5% red 87.5% green

and we need to be able to distinguish the levels 10%, 37.5% 62.5% and 87.5% in red and 12.5%, 37.5%, 62.5% and 90% in green.

But if there are more than two positions, or two choices at those positions, then we need to have finer gradations. Bear in mind that merely contacting an aliquot of carriers with a mixture of 75% red particles/25% green particles does not guarantee that every carrier in the aliquot will thereby acquire particles in exactly that 75:25 ratio. Hence, there are practical limits to reducing the size of the gradations.

Certainly, there is no showing that Trau permits individual identification of beads in the numbers contemplated by claims 33-37.

In any event, in contrast to the beads of our preferred embodiments, the beads disclosed by Trau are <u>not</u> individually identifiable by measurement of a set of positional coordinates for the component particles. New claim 106 requires that the

composition be "suitable for individual identification of said beads by determination of the spatial positions of said particles" to further distinguish Trau. Likewise, new claims 109-111, dependent on 33-35, require that "each bead is individually identified by the relative spatial positions of the particles embedded within said bead".

Localization of particles

Another feature that distinguishes the composition according to present invention and the composition disclosed by Trau is the localization of the particles. The present invention discloses particles that generally speaking are embedded in the beads, whereas Trau discloses particles that generally speaking are attached to the surface of the beads.

Our application cited the following regarding the localization of the particles **inside** the beads:

Page 18 lines 6 to 8: "Each bead is uniquely identified by an orientation independent distance matrix describing the relative positions of particles within the encoded bead".

Page 15 lines 21 to 22: "The coordinates are relative spatial coordinates assigned to particles in the bead".

Page 15 lines 3 to 4: "Beaded polymer matrix: A beaded polymer matrix is a crosslinked polymer formed by beading according to principles of suspension or inverse suspension polymerization, by spray polymerization, or by droplet polymerisation".

Page 17 lines 18 to 19:"Spatially immobilised particles: Particles which are immobilized in a surrounding polymer matrix in such a way that the individual distances between the immobilized particles are constant in a particular solvent".

Example 1 and 2 in the present application discloses how the particles are embedded inside the beads - i.e. the beads are prepared by inverse suspension polymerisation methods. In other words, a solution of particles is polymerized to generate beads with particles embedded inside.

Trau teaches that premade carriers ("beads") are mixed with the reporter beads ("particles") - c.f. e.g. Example 3, and hence the particles are expected to be attached to the outside of the beads. Surface coatings are taught to facilitate such attachment.

We acknowledge that Trau teaches "It will be appreciated that reporter beads may be attached to the surface of a carrier but this is not essential. In this regard, the inventors recognise that it would be possible to attach reporter beads to the inside of a carrier through existing pores of the carrier."

However, it is not at all clear that the Trau's carrier in fact has pores large enough to permit entry of the reporter beads. Nor is it clear that there would be a significant degree of pore penetration under the conditions taught by Trau. It is doubtful that the teaching has the enabling character appropriate for an anticipation rejection. Note that Trau teaches carriers of 1-1000 microns and reporter beads of 0.01-50 microns; his larger reporter beads are larger than his smaller carriers. Trau does not teach what is the appropriate maximum pore size for a given size carrier.

Also, claim 32 requires that the particles be "held" in the polymer matrix, and if Trau's particles enter the pores, then conceivably they could escape the pores the same way they entered. Hence, we do not think that they are "held" within the meaning of claim 32.

Moreover, even if some reporter beads (particles) managed to enter the pores, it is likely that many, even most, of the particles would remain on the surface of the carrier. New

claim 107 requires that essentially all of the particles are embedded within the beads. (As to the propriety of "essentially", please see the discussion of the teachings of the specification and the case law in section 4.1, and note that the teachings of how to make our beads provides a "standard for comparison", showing when "essentially all beads are embedded".)

New claim 108 requires that "said beads are obtainable by suspending the particles in a polymerizable liquid, polymerizing the liquid to obtain the polymer matrix, and forming beads with embedded particles from said matrix". Such process would of course result in the particles being generally embedded in the beads.

We further note that even if it were contrived to introduce the reporter beads (particles) into the pores of the carrier, the spatial positions of the reporter beads (particles) would be limited to those accessible by means of those pores. This in turn limits the number of unique codes derivable from the spatial positions of the particles.

9. Obviousness Issues

9.1 OA s31 rejects claims 2, 3, 7-12, 17-40 and 42 as allegedly obvious over Trau et al. WO 99/24458 and Frankel US 6,506,342. We traverse.

The Examiner conceded that "Trau et al. does not teach a specific number of carriers", as required by claims 33-37. Hence, the Examiner cited Frankel, US 6,506,342, which discloses bead libraries comprising 10^2-10^6 beads, greater than 10^8 beads, or greater than 10^9 beads (column 2 and 9).

However, as explained in the previous section, Trau does not anticipate the claims because Trau does not meet the particles-per-bead limitation of claim 32.

Frankel tags each bead with a "distinct ID tag" that makes use of an "electromagnetic spectral code". Col. 6, lines

44-46. The ID tag is composed of a plurality of narrow bandwidth electromagnetic spectrum emitters. Cols. 11-12. By way of example, Frankel says that if 6 out of 30 possible emission frequencies were used in combination to tag each bead, then 493,775 unique identification codes are possible. Col. 11, lines 55-60. While 6 is within the range 3-10 recited in claim 32, Frankel's emitters are not "particles" and also they do not have "a diameter of less than 30 micrometers" as required by claim 32.

The spatial encoding principle we claim is very different from the spectral encoding principle disclosed by Frankel.

In particular, claim 32 is limited to particles with a diameter of less than 30 microns. In contrast, Frankel discloses beads comprising:

- planar disc shaped electromagnetic spectrum emitters of thickness 80-250 microns and diameter 100-1000 microns (see e.g. col.18, l.48-53; col.19, l.51-54; col.20, l.13; col.20, l.45-46; col.20, l.50-51; col.20, l.63-65), or

- rectangular electromagnetic spectrum emitters of dimensions in the range 10 X 50 X 600 to 10 X 50 X 1000 microns (col.25, l.63-64; col.26, l.44-45), or

- electromagnetic spectrum emitters comprising spherical **microcavities** with diameters in the range of from 5 to 20 microns (col.27, l.53-54)

The bead e.g. illustrated in Fig. 16 and described in col. 27 in Frankel represents a different coding principle as compared to our invention. Our beads comprise particles, whereas Frankel's beads as e.g. illustrated in Fig. 16 comprise cavities. Frankel's code as illustrated in Fig. 16 will only work with cavities and not with particles. In further embodiments, Frankel discloses electromagnetic

spectrum emitters which have a diameter larger than the maximum 30 micron particle diameter we cite in claim 32.

We recognize that Trau WO 99/24458 teaches particles with a size range (0.01 - 50 microns, see P19, L2-3; 1 micron in Examples) that includes the range recited in our claim 32.

However, the examiner cannot pick and choose, with the benefit of hindsight, which aspects of Trau's particles to keep and which to replace with those of Frankel's emitters. If Trau's particles are replaced with Frankel's emitters, the number of emitters may be comparable to the number of claim 32's particles, but the emitters are cavities not particles, and are also larger than what is demanded by claim 32.

9.2. OS s32 rejects claims 7-11, 25, 26, 32, 38-40, and 42 as allegedly obvious over Nilsson et al. US 5,015,576. We traverse.

US 5,015,576 discloses particles or macroporous beads which enclose cavities comprising water-insoluble solid, cells or other particles. The diameter of the particles and cavities are 10 to 5000 micrometer and 1 to 50 micrometer, respectively (abstract and column 3 lines 22 to 36). Nowhere does US 5,015,576 disclose that these beads have from 3 to 10 spatially immobilized, individually detectable particles held in a polymer matrix.

In a specific embodiment - Example 9 - Nilsson discloses that "the sizes of the beads could be between 10 and 500 micrometers" and that "each bead has to be provided with a minimum number of cells (usually 5-10 cells/bead)". However, the sizes of the beads (between 10 and 500 micrometers) falls outside (or at best touches) the range cited in claim 32 of the present patent application (i.e. 0.5 millimeter to less than 2.0 millimeter).

In any event, nowhere does Nilsson disclose beads with a diameter of from 0.5 millimeter to less than 2.0 millimeter

having from 3 to 10 spatially immobilized, individually detectable particles held in a polymer matrix.

The Examiner states in the outstanding Office Action that the claims of the present invention "would have been obvious because the substitution of one known element (i.e. unknown number of particles and specific polymer taught by Nilsson et al.) for another (i.e. another particle number or another polymer; see petition decision by Julie Burke wherein QAS Burke stated that all particle numbers and polymers would be obvious variants)".

Respectfully, QAS Burke is not a person skilled in this art and therefore is not the best judge as to whether all particle numbers would be obvious variants over each other.

Practical measurements reveal the difficulty of identifying encoded beads having a high detectable particle density - i.e. more than about 350 detectable particles per microliter. This is due to the fact that the probability of encountering what is known as "correspondence problems" increases with an increasing detectable particle density.

The correspondence problem can broadly be described as the problem of distinguishing two different encoded beads from each other. Correspondence problems will arise when the three-dimensional (3D) positions of detectable particles inside an encoded bead are to be determined based on two or more images (projections) of the encoded bead recorded from different angles. In short, a correspondence problem arises when two or more encoded beads harbouring spatially immobilised microparticles cannot be unambiguously identified from images of the spatially immobilised detectable particles obtained from different angles.

The correspondence problem is illustrated in Figs. 10, 11 and 19, and an experimental evaluation of the significance of the problem is presented on pages 23-25 in the present application. It is clear that the number of beads having a correspondence problem correlates positively with an increased

number of microparticles per bead, i.e. an increased detectable particle density.

Accordingly, it will be increasingly difficult to overcome and solve a correspondence problem when the number of spatially immobilised detectable particles is increased from e.g. 10 to e.g. 25. This can be seen e.g. from the simulation disclosed in the top part of Fig. 11 illustrating the number of spatially encoded beads with a "correspondence problem". The simulation experiment is described in more detail on pages 23-25 in the description.

The technical problem to be solved can be formulated e.g. as how to achieve a better identification, or a more simple or easy identification, of a spatially encoded bead, c.f. page 5, lines 27-30, of the description of the present application.

Page 69 lines 31 to 35 further states the following regarding the correspondence problem:

> *"It further appears from the figure that the number of encoded beads with correspondence problem increases with increasing average number of immobilised particles per encoded bead, whereas the number of not identified encoded beads does not vary significantly with the average number of immobilised particles per encoded bead".*

In order to overcome the above stated technical problem one can - in principle - either

a) invent a more sensitive method which aims to overcome one or more of the problems stated in the state of the art, and/or

b) invent spatially encoded beads which are more readily identifiable than state of the art encoded beads using state of the art identification methods.

The present application - in relation to a) above - discloses on pages 21 and 22 of the description three approaches which can be used to increase the sensitivity of a state of the art method for encoded bead identification.

Furthermore, in relation to b) above, claim 32 is directed to a low detectable particle density encoded bead which differs from the state of the art encoded beads.

Nowhere in the prior art can the skilled person obtain any guidance as to the relationship between bead diameter and microparticle number. Accordingly, the skilled person is unable to evaluate whether the detectable particle density should be increased, or decreased, or remain the same, when the bead diameter is changed. In other words the prior art does not teach or suggest the advantage of larger bead size and fewer microparticles - the result being a much lower detectable particle density.

In summary, the inventive step associated with claim 32 and the claims dependent thereon should be acknowledged. Nowhere can the skilled person find any guidance for the solution proposed by the present invention: spatially encoded, individually identifiable beads having a larger size and a lower detectable particle density.

Respectfully submitted,

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